REMARKS

This communication is filed in response to the Non-Final Rejection mailed October 17, 2008. Claims 1-4, 8, 9, 11 and 12 are currently pending. Claims 5-7, 10, and 13-42 have been cancelled without prejudice according to the Examiner's request on page 2 of the Office Action. Claims 1, 3, 8 and 9 have been amended. The support for the amendments is found at least in the originally filed claims, Example 2 *et seq.*, and in paragraph 0118 *et seq.* of the application as filed. No new matter is introduced into the application with this response.

Applicants' invention is directed to *inter alia* a composition comprising a reaction mixture comprising a complex of an NS1 protein of influenza virus, or a dsRNA binding fragment thereof, and a synthetic dsRNA of about 16 base pairs in length that binds the NS1 protein. The references cited by the Examiner do not disclose compositions of influenza virus NS1 protein and dsRNA of about 16 base pairs in length. The dsRNA targets of Applicants' invention are either short dsRNA of about 16 base pairs in length or single-stranded RNA comprising a hairpin dsRNA structure formed by intramolecular base pairing.

A. Rejection based on 35 U.S.C. § 102(b) or 35 U.S.C. § 103

The Examiner rejected the claims 1-4, 8, 9, 11 and 12 of the instant application as allegedly anticipated by or in the alternative, obvious over Wang et al., *Virology*, 233:41 (1996) ("Wang"). The Examiner has also rejected claims 1-4, 8, 9, 11 and 12 of the instant application as allegedly anticipated by or in the alternative, obvious over Lu et al., *Virology*, 214:222-228 (1995) ("Lu"). Applicants respectfully traverse. Since the disclosures of Wang and Lu are very similar and since the Examiner uses essentially the same arguments as the basis for rejecting the claims over each reference, both rejections will be addressed together for the purpose of efficiency.

Wang discloses an influenza virus NS1 protein binding to a large dsRNA polynucleotide sequence of 55 bp long (Wang, page 43). Lu discloses NS1 binding to a 29 bp long dsRNA and also discloses labeled fusion protein to NS1. Thus, in applicability of these references to the analysis of patentability of claim 1, the disclosures of Wang and Lu are essentially identical except the length of dsRNA used in these references. In Wang, the length is 55 bases, in Lu, it is 29 bases.

In contrast, claim1 and the dependent claims 2-4, 8, 9, 11 and 12 define the synthetic dsRNA sequence as a short sequence of about 16 base pairs. Clearly, the dsRNA sequence of the instant application is never present in the disclosures of Lu and Wang, let alone, necessarily and always present, as required for the inherent anticipation. See, e.g., MPEP § 2113.IV, stating, in relevant part, that "[t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." If the Examiner contends that the 16 bp dsRNA of the instant invention is indeed necessarily present in the disclosures of Wang and Lu, it is his burden to explain why. See, e.g., MPEP § 2113.IV ("In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art") emphasis in MPEP, internal quotation omitted. Accordingly, for at least this reason, the claims of the instant invention are not anticipated by either Wang nor Lu.

Applicants further submit that Lu and Wang do not render the claims of the instant application obvious. In making his argument of obviousness, the Examiner relies on the disclosure on p. 21, lns 28-29, which disclosure states, in relevant part, that the length and the sequence of the dsRNA is not crucial. Applicants respectfully submit that such reliance is misplaced. The aforementioned sentence is not an admission, contrary to the Examiner's assertion on pages 5 and 7 of the Office Action. Instead, this sentence is an inference made in view of the results disclosed in the instant application. As discussed in details below, the belief of the scientific community at the time of the invention was that the length of the dsRNA is an important factor for the formation of complex with NS1.

Applicants respectfully submit a Declaration by Dr. Krug, who is a senior co-author of the Lu and Wang publications. Applicants respectfully request that the Examiner to give this declaration considerable deference because the conclusions of the declaration are supported by evidence and solid scientific reasons. See MPEP § 716.01(c) (expert opinion on what the prior art taught, supported by documentary evidence and formulated prior to the making of the claimed invention, received considerable deference, quoting from *In re Carroll*, 601 F.2d 1184, 202 USPQ 571 (CCPA 1979)).

As established by the Declaration, at the time of the work by Wang et al, it was believed that the cooperative binding of multiple NS1 protein molecules to a large dsRNA was required in

order to have sufficiently tight binding to detect in gel shift experiments, like those shown in Wang or Lu. The reason for this belief was readily apparent in Wang where it was shown that there was a large decrease in binding affinity when the size of the RNA target was reduced from 140 to 55 bps; and in Lu, where it required a high concentration (4 micromolar) to obtain a gel shift with a 29 bp dsRNA. Accordingly, the use of relatively short dsRNA for detection and quantification of binding between such dsRNA and NS1 or dsRNA binding fragment thereof was contrary to scientific theories at the time of the filing date of the instant patent application. According to MPEP § 2145.X.D.3, "proceeding contrary to accepted wisdom in the art is evidence of nonobviousness."

Applicants further submit that in view of the results of Wang demonstrating that there was a large decrease in binding affinity when the size of the RNA target was reduced from 140 to 55 bps; and the results of Lu, where a high concentration (4 micromolar) was required to obtain a gel shift with a 29 bp dsRNA, it was not predictable from Wang or Lu that a small about 16 bp dsRNA could provide sufficiently tight binding to allow a feasible high throughput assay, as discussed in Dr. Krug's declaration.

Applicants' discovery that a short dsRNA (e.g., dsRNA having about 16 bp in length) is suitable for the binding assays makes the present invention significant. From purely scientific perspective, the unexpected finding that short 16 bp dsRNA binds NS1 or the dsRNA binding fragment thereof sufficiently tightly (tighter than ~ 1 micromolar) is sufficient to rebut, or at the very least, to doubt the semi-cooperative binding theory.

From the applied science perspective, the Applicants' discovery allows significant and advantageous applications of the compositions of the instant invention, which would not be available based on the prior art, e.g., Lu or Wang.

For example, high throughput assays could be conducted using the claimed composition. In this case, the obstacle which the prior art had to overcome is not purely the cost of synthesizing the 29 or 55 bp long dsRNA, which is undoubtedly much higher than the cost of manufacturing the dRNA of about 16 basepairs. Certain assays, such as fluorescence polarization assay, may be conducted more reliably using the 16 bp dsRNA than the 29 or 55 bp long dsRNAs of Lu and Wang. Essentially, the amplitude of the signal is much smaller upon complex formation when using a large RNA molecule than when using a smaller ~ 16 bp dsRNA, since binding of the smaller ~ 16 bp dsRNA results in a larger change in rotational

correlation time than binding a larger fragment. These issues have been recognized, for example, in Nasir, M.S., Jolley, M.E. Fluorescence polarization: an analytical tool for immunoassay and drug discovery, *Comb. Chem. High Throughput Screen* 2 (1999) 177–190 and in Rochrl, M. H. A., Wang, J. Y., and Wagner, G., A general framework for development and data analysis of competitive high-throughput screens for small-molecule inhibitors of protein-protein interactions by fluorescence polarization, *Biochemistry 43*, 16056-16066 (2004). Thus, the kits and methods utilizing the compositions of the instant invention would not have been commercially feasible, or even possible, without the Applicants' surprising discovery that short dsRNA molecules are sufficient for NS1 binding.

In addition, the shorter dsRNA molecule of the instant claims is easier to synthesize than its 55 base pair counterpart. Applicants submit that it would not be possible, or at the very least, much more difficult and expensive, to prepare these large biosynthetic dsRNA, or similar large RNAs, in sufficient quantities to use in the assays. In screening of drug candidates, in particular in high throughput screening experiments, the availability of materials and the convenience in use of such materials are important factors to the efficiency of the experiments.

In summary, Applicants' invention is contrary to the accepted scientific thought at the time of filing, and therefore, the Applicant's results are highly unexpected. Further, the instant invention allows detection of the dsRNA-NS1 complex using methods previously thought unsuitable for this purpose, e.g., fluorescence polarization assay. Finally, the instant invention results in more economically efficient assays for screening for compounds affecting binding between dsRNA and NS1.

Therefore, in view of the reasons above, Applicants respectfully submit that the discovery of suitability of the shorter synthetic dsRNA sequence is itself a beneficial, surprising result, and therefore claims 1-4, 8, 9, 11 and 12 are allowable.

CONCLUSION

Applicants respectfully submit that the pending claims are valid and favorable reconsideration and allowance are earnestly solicited. If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that the Examiner telephone Applicant's attorney at (609) 844-3020 to discuss any additional rejections.

The USPTO is authorized to charge Deposit Account No. 50-1943 for any fees due.

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Respectfully submitted,

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